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Asymmetric Imine Isomerisation in the Enantioselective Synthesis of Chiral Amines from Prochiral Ketones

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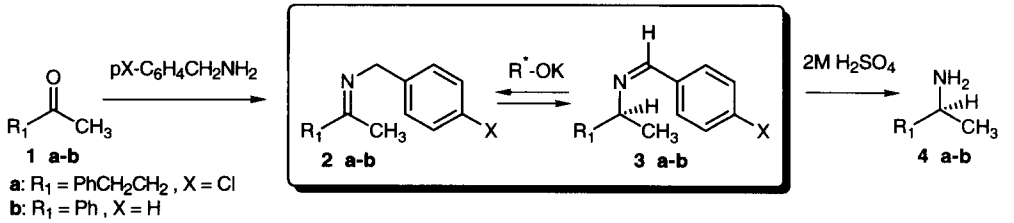
Abstract: An asymmetric catalytic synthesis of chiral amines using a chiral base catalysed [1,3]-proton shift reaction of imines is described. The isomerisation reaction of N-benzylimines **2a-b** derived from prochiral ketones (benzylacetone, acetophenone) and p-substituted benzylamines, is catalysed by chiral alcohols and aminoalcohols **5-12** and gives enantiomerically enriched (up to 44% e.e.) N-benzylidene derivatives **3a-b**. The resulting products **3a-b** are readily hydrolysed to their corresponding amines **4a-b**.

One of the synthetic approaches towards optically active amines is the asymmetric reductive amination of a prochiral ketone[1]. Until now only a limited number of examples have been reported involving the enantioselective hydrogenation of imines (e.e.'s up to 98%), although the resulting chiral amines are important intermediates for pharmaceutical products and have found use as resolving agents. An alternative route towards optically active amines using imine intermediates is the asymmetric [1,3]-proton shift imine isomerisation by chiral bases as depicted in scheme 1. This imine isomerisation reaction (methylene azomethine rearrangement), was extensively studied by Ingold et al.[2] in the 1930s and by Cram et al.[3] in the 1960-70s using achiral bases.

In this letter we report our preliminary results concerning the enantioselective [1,3]-proton transfer in the azaallylic system of N-benzylimines **2a-b** catalysed by chiral bases (**5-12**) which results in the formation of thermodynamically favoured N-benzylidene derivatives **3a-b**.



Scheme 1

We have checked the catalytic abilities of several chiral alcoholates in this reaction, namely those derived from (-)-N-methylephedrine (**5**), (-)-N-tritylephedrine (**6**), (2S)-N-trityl-aziridine diphenylcarbinol (**7**), quinine (**8**), quinidine (**9**), L(-)-menthol (**10**), L(-)-8-phenylmenthol (**11**) and L(-)-borneol (**12**) (Figure 1).
All imine isomerisation reactions were performed in THF or toluene in the presence of 30 mol % of chiral alcoholate catalyst. These chiral catalysts were obtained by treatment of the corresponding alcohols **5-12** with 1 equiv. of KH in THF or toluene for 60 min. at 70°C. Subsequently the imine substrates were added. The reactions were monitored using GLC and HPLC[4] and the percentage of conversion and the e.e.'s were

determined during the imine isomerisation process. It was found that in the case of imine **2a**, derived from benzylacetone and p-chloro-benzylamine, almost no racemisation of the imine product **3a** occurred under the reaction conditions applied. (Figure 2).

However, during the asymmetric isomerisation of imine **2b**, derived from acetophenone and benzylamine, initial e.e.'s were also the maximum values, because during the reversible imine isomerisation process racemisation of the product **3b** took place (Figure 3).

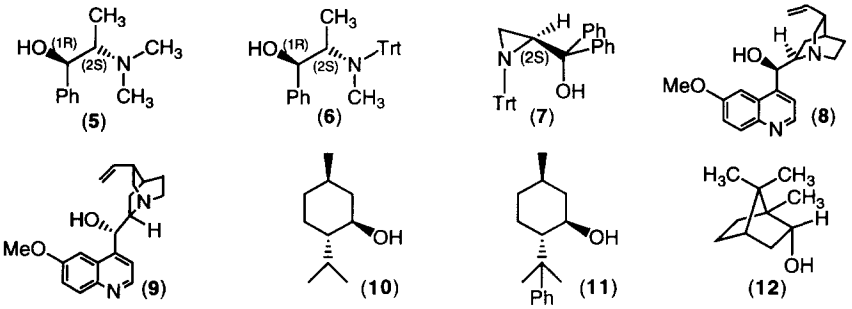
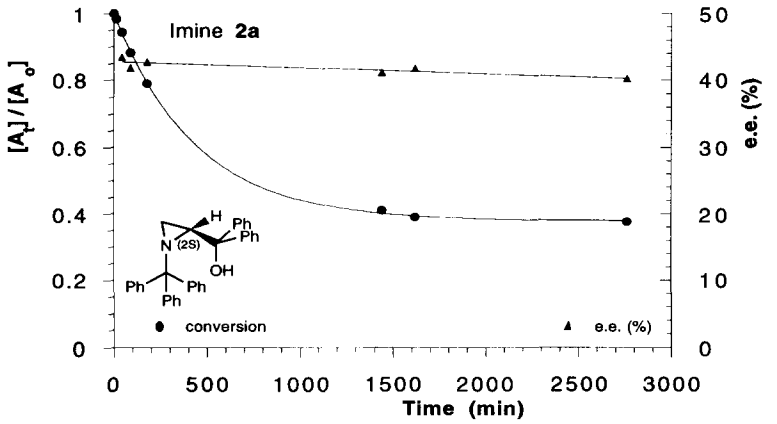


Figure 1

The imine isomerisation reaction can be described by first order equilibrium kinetics and $k_{overall}$, k_1 and k_{-1}-values could be determined from the collected data. Typical examples of a conversion versus time and e.e. versus time plot for the asymmetric imine isomerisation of **2a** and **2b** using the potassium alcoholate derived from **7** in toluene as the catalysts are shown in Figures 2-3. Comparison of the imine isomerisation reaction of imines **2a** and **2b**, using the same solvent and chiral amino alcoholate catalyst **7**, shows that the isomerisation reaction of imine **2b** is much faster than that of imine **2a**. In the case of **2a** it was necessary to heat the reaction mixture to 105°C because at lower temperatures only a low conversion of **2a** into **3a** occurred.

Figure 2. Asymmetric imine isomerisation of imine **2a** using chiral potassium alcoholate derived from **7**.



● $[A_t] / [A_0]$ = {100 - conversion(%)} / 100 measured by GLC and ▲ e.e (%) = enantiomeric excess of **3a** measured by HPLC as a function of time. Reaction conditions: [imine **2a**] = 0.2 mmol/mL, [catalyst **7**] = 0.06 mmol/mL (0.3 equiv), solvent: toluene, temperature: 105°C.

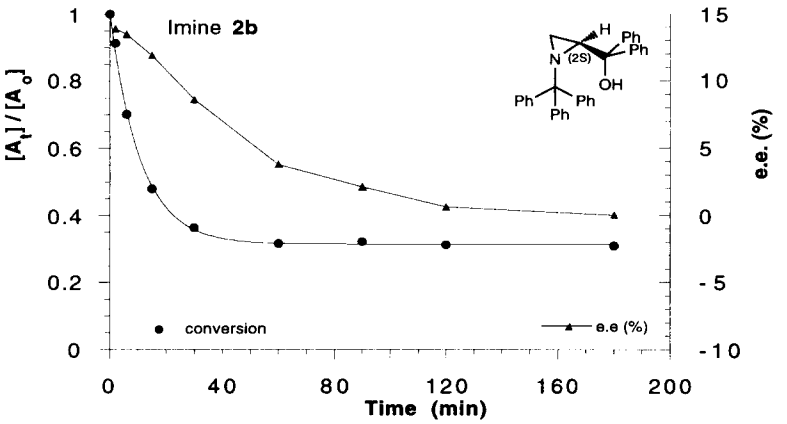
The reason for this slower isomerisation reaction of **2a** in comparison with **2b** is possibly due to the fact that imine **2b** is able to form a more stable aza-allyl anion intermediate than imine **2a**. The chiral potassium

alcoholate catalysts **5-9** were effective in catalysing the transformation of **2a-b** to **3a-b**. The chiral potassium alcoholates derived from **10-12** gave imine isomerisation reactions for imines **2a-b** in THF and toluene, but the e.e.'s were very low (0-3%) (Table 1). From these results it was concluded that chiral alcohols are not the catalysts of choice in the asymmetric imine isomerisation reaction.

When Li^+ and Na^+ were used instead of K^+ counterions no imine isomerisation reaction occurred.

Comparison of the inducing ability of the catalysts using different solvents under otherwise similar reaction conditions showed that in most cases higher e.e.'s were obtained in toluene than in THF (Table 1), but in all cases the reaction rate was lowered in toluene (Table 1). The highest e.e.'s (22-44%, entries 4-5) were observed for the isomerisation of imine **2a** using the potassium alcoholate derived from **7** as the chiral base in toluene as the solvent (Figure 2). Carbinol **7** was synthesised in a 4 step procedure starting from L-Serine[5]. The trityl group in catalyst **7** was considered of importance and therefore (-)-N-tritylephedrine (**6**) was synthesised starting from commercially available (-)-ephedrine. The maximum e.e.'s in the isomerisation of **2b** using amino-alcoholates derived from **6** and **7** were of the same order (14%, entries 13-14).

Figure 3. Asymmetric imine isomerisation of imine **2b** using chiral potassium alcoholate derived from **7**.



● $[A_t] / [A_0]$ = {100 - conversion(%)} / 100 measured by GLC and ▲ e.e (%) = enantiomeric excess of **3b** measured by HPLC as a function of time. Reaction conditions: [imine **2b**] = 0.2 mmol/mL, [catalyst **7**] = 0.06 mmol/mL (0.3 equiv), solvent: toluene, temperature: 22°C.

However, isomerisation of imine **2a** using the alcoholate catalyst derived from (-)-N-tritylephedrine (**6**) led to a much lower e.e. than the imine isomerisation with the alcoholate from **7**. Apparently, the enantioselectivity is both substrate and catalyst dependent.

When isomerisation reactions of imine **2b** were performed in THF at room temperature a fast reaction took place and no asymmetric induction of the product imine was observed. Changing from THF to toluene using the same chiral alcoholate bases (**5-10**), slowed down the imine isomerisation reaction, as was also observed for imine **2a**, and in all cases the reaction proceeded in an asymmetric fashion (e.e. = 2-14%, entries 12-16).

The crude product mixtures of imines **2a-b** and **3a-b** were hydrolysed after equilibrium was reached using 2M sulphuric acid, and the product amines **4a-b** together with the p-substituted benzylamines were isolated using acid-base extraction in good yields (85-95%). The crude product mixtures were not purified but analysed by NMR, IR and GC/MS as such. After hydrolysis the e.e. of the crude amine **4a** (entry 4) was checked by GLC (Mosher acid chloride derivative) and HPLC (benzaldehyde derived imine derivative) using a chiral column (Chiralpak AD). The e.e. of amine **4a**, obtained after hydrolysis of **3a**, was identical with the e.e of imine **3a** before hydrolysis (Figure 2), implying that no racemisation had occurred during the hydrolysis and work-up

procedure. For amine **4b** (entry 14) the same procedure as described for **4a** was followed, yielding an amine product **4b** that had been racemised under the imine isomerisation reaction conditions applied. (Figure 3).

In conclusion, we have developed a general method for the catalytic asymmetric synthesis of chiral amines via a [1,3]-proton transfer reaction. Soloshonok et al. recently described the asymmetric isomerisation[6] of imines derived from β-polyfluoroalkyl-β-ketocarboxylic esters and benzylamine, a special class of imines, using (-)-cinchonidine as the base in solvent free reaction conditions and high temperatures. Since their procedure can only be applied in the case of imines derived from β-keto-esters, we believe that our method is more generally applicable in the asymmetric [1,3]-proton shift reaction.

Table 1. Asymmetric imine isomerisation using chiral potassium alcoholates derived from **5-12**

Entry	R_1	Reaction Conditions[a]			$t_{1/2}$ min[b]	e.e.$_{max}$ (%)[c] (Config)[c]
		Base	Solvent	Temp,°C		
1	(**1a**) $PhCH_2CH_2$	**5**	THF	66	60	7 (R)
2	(**1a**) $PhCH_2CH_2$	**5**	toluene	105	450	10 (R)
3	(**1a**) $PhCH_2CH_2$	**6**	toluene	105	400	2 (R)
4	(**1a**) $PhCH_2CH_2$	**7**	THF	66	100	22 (S)
5	(**1a**) $PhCH_2CH_2$	**7**	toluene	105	300	44 (S)
6	(**1a**) $PhCH_2CH_2$	**8**	THF	66	40	5 (R)
7	(**1a**) $PhCH_2CH_2$	**9**	THF	66	40	5 (S)
8	(**1a**) $PhCH_2CH_2$	**10**[d]	THF	20	40	3 (S)
9	(**1a**) $PhCH_2CH_2$	**10**	toluene	90	40	3 (S)
10	(**1a**) $PhCH_2CH_2$	**11**[e]	THF	66	12	2 (S)
11	(**1a**) $PhCH_2CH_2$	**12**[f]	THF	20	50	2 (S)
12	(**1b**) Ph	**5**	toluene	20	5	6 (R)
13	(**1b**) Ph	**6**	toluene	20	18	13 (R)
14	(**1b**) Ph	**7**	toluene	20	8	14 (S)
15	(**1b**) Ph	**8**	toluene	20	60	11 (S)
16	(**1b**) Ph	**10**[g]	toluene	20	4	2 (S)

a) Concentration of potassium salt of catalysts **5-12** is 30 mol % and concentration of imine is 0.2 mmol/mL. b) The parameter $t_{1/2}$ is the reaction time for 50% conversion of the starting material. c) e.e. of **3a-b** determined by HPLC (Daicel Chiralpak AD) (eluent: hexane / 2-propanol = 98 : 2, v/v). d) **[10]** = 60 mol %. e) **[11]** = 20 mol %. f) **[12]** = 95 mol %. g) D(+)-menthol was used.

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4. HPLC analysis was performed on the crude imine reaction samples after quenching with 50% NaOH / ether using a Daicel Chiralpak AD Column (eluent: hexane / 2-propanol = 98:2, v/v).
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